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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FISH & RICHARDSON P.C.
P.O BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
POHNERT, STEVEN C	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,688	AMBROSE ET AL.	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-9 and 11-31* is/are pending in the application.

4a) Of the above claim(s) *5-9 and 11-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 15-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/9/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group 1, claims 1-3 and new claims 15-31, as drawn to SEQ ID NO 16 with a cytosine at position 811 in the reply filed on 10/10/2006 is acknowledged. The traversal is on the ground(s) that, "Comparison of the amino acid sequences in Laubert (SEQ ID NOs: 3-10) with Applicants' SEQ ID NO: 17 (the amino acid sequence of OATP8) indicates that while Laubert may describe a member of the OATP protein family, this reference does not appear to describe OATP8. Amino acid differences between SEQ ID NO: 17 in Applicants' specification and SEQ ID NO:3 of Laubert et al. occur at least at positions 13-15, 18, 23, 27, 36, 38, 42, 45, 51, and 53." This is not found persuasive because although the amino acid sequence taught by Laubert (WO2000/08157) is not identical to the SEQ ID NO 17, the nucleotide sequence of the SEQ ID NO 1 of Laubert has over 99% identity with SEQ ID NO 16 of present invention and has a G at position 811 (see attached alignment). Thus the sequence of SEQ ID NO 16 has no technical feature over the prior art.

2. Claims 5-9, 11-14, withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/10/2006.

The requirement is still deemed proper and is therefore made FINAL.

A first action on the merits of claims 1-3 and 15-31 follows.

Specification

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Detection of a Polymorphism in the OATP8 Gene

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 19- 26 and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In claim 15 and 19, the recitation "in need of treatment with a therapeutic agent that is transported by OATP8" appears to be new matter. The specification does not provide basis for the concept of therapeutic agent transportable by OATP8. The remarks filed with the amendment cite basis for claim 15 and 19 at pages 3 and 4. The cited recitation on page 3 (lines 23-31) and page 4 (lines 5-7) do not mention therapeutic agents. These sections do not teach therapeutic agents that are transported by OATP8. Since the specification does not teach drugs that are

"transported" by OATP8, the claims are rejected for having new matter. Claims 20-26 depend from claim 19, and these claims are also rejected for containing this new matter.

With regard to claims 22, 24, and 30, the new limitation of "the nucleotide is not an G" in claim 22 and 30 and the recitation "the nucleotide is in a codon that does not encode a glycine" in claim 24 appear to represent new matter. In applicant's remarks filed with the amendment, applicant asserts that support for these claims can be found on page 18 in the second table. This provides basis for a limitation wherein the nucleotide at position 811 of SEQ ID NO: 16 is an G or a C, however none of them provide specific basis for the limitation that the nucleotide is "not an G" or that the codon "does not encode a glycine." The table at page 18 recites "811 G→C." The language of these claims encompasses additional alleles at this position, and claim 24 additionally encompasses changes in the other nucleotides that are within the codon that position 811 is a part of, providing that the changed "codon does not encode an glycine." Specifically, the exclusionary proviso in which the nucleotide is "not an G" or "does nor encode an glycine" is not found in the specification. As noted by MPEP 2173.05(i),

> "Any negative limitation or exclusionary proviso must have basis in the original disclosure. See Ex parte Grasselli , 231 USPQ 393 (Bd. App. 1983) aff'd mem., 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement."

Since no explicit basis has been identified for the newly added negative limitation, claims 22, 24, and 30 are rejected as incorporating new matter.

6. Claims 1-3 and 15-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors have been described by the court in re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Nature of the Invention and Breadth of the Claims

The claims are all drawn to methods of detecting a single nucleotide polymorphism within the human OATP8 gene. The particular polymorphism is an G→C transition at position 811 of SEQ ID NO: 16, which is the nucleotide sequence encoding

human OATP8. Claims 1-3, 27 set forth detecting a polymorphism in a human by determining the nucleotide present at position 811 of SEQ ID NO: 16. Thus, the "use" of this invention requires the knowledge of the relationship between the polymorphism at position 811 of SEQ ID NO: 16 and some phenotype, for example, a disease or response to a drug.

Rejected claims 15-26, 28-31 require that the nucleic acid sample assayed be obtained from an individual identified as "in need of treatment with a therapeutic agent that is transported by OÂTP8." Thus, the nature of the invention requires the knowledge of drugs that are transported by OATP8. Further, the implication of the claim is that the identity of the nucleotide will be useful for determining treatment for the human, and indeed, the specification states that "preferably determination of the status of the human is clinically useful (p. 14, line 4)," describing such utilities as determining what drug to administer or effective amounts of drugs. Most of the claims are sufficiently broad so as to encompass any possible drug that is "transported by OATP8," and any reason for treatment with such a drug.

State of the Art

The prior art teaches the nucleic acid sequence of the cDNA of the human OATP8, and that this molecule is a member of the OATP transporter family (Iida et al., Journal of human Genetics (2001) volume 46, pages 668-683). Iida et al. further teach that OATP8 transports typical organic anions, but not bile salt (p. 668, column 1, lines

38-39). This transport profile is different from the closely related OATP2 (p. 668, column 1, lines 38-39).

The prior art does not teach that any particular diseases are mediated by OATP8. The prior art does not demonstrate any polymorphisms within OATP8 that are indicators of disease or of response to drug treatment. The prior art does not establish any relationship between OATP8 and statin efficacy.

Direction Provided and Working Examples

The specification provides a brief summary of the knowledge in the prior art concerning OATP8 (p. 1), and teaches the identification of a SNP within SEQ ID NO: 16, namely, a G→C transition at position 811 of SEQ ID NO: 16. The specification teaches that this SNP results in a transition from gly→ala in the encoded polypeptide. The specification teaches that OATPC has been shown to be involved in the transport of statins (p. 14, line 16), but the specification is silent as to the transport of statins by OATP8. The specification does not provide any further guidance as to how any diseases are in fact mediated by OATP8, or how to identify a risk of having such diseases. The specification does not provide any working examples of methods for identifying patients as having or at risk of having OATP8 mediated disorders, or of using the identity of the nucleotide at position 811 of SEQ ID NO: 16 for selecting medications for a patient. Furthermore, the specification does not disclose any relationship between OATP8 mediated diseases and the polymorphism at position 811 of SEQ ID NO: 16. While the specification does refer generically to "OATP8 mediated" disorders, the

specification does not particularly define what is required for a disease to be mediated by OATP8.

The amount of direction or guidance presented in the specification with regard to how to use the instant invention is minimal. That is, the specification does not provide any guidance as to how the polymorphism at position 811 of SEQ ID NO: 16 would be associated with any pharmaceutical agent. The specification does not discuss whether this particular polymorphism will increase the likelihood of a positive or negative response to any drug. The specification provides no guidance or working examples that teach or demonstrate the ability to use the disclosed polymorphic site as a marker for any disease in particular, or for disease in general, or how to use the disclosed polymorphism to select a proper course of treatment of a disease.

Level of Skill in the art, Level of Unpredictability, and Quantity of Experimentation

The level of skill in the art is quite high, but the unpredictability in the art is higher. There is no way of predicting which diseases, of the variety of possibilities proposed in the specification, as well as of the variety of diseases and disorders generally known, are in fact "OATP8 mediated." The prior art of Iida et al. demonstrated that OATP8 does not have an identical activity profile as other OATP molecules, in particular as OATPC. Further, the post-filing date art of Letschert et al. exemplify the unpredictable nature of this art area (Letschert et al. Pharmacogenetics, 2004, 14:441-452). They teach that mutations in OAT1B3 (OATP8) abolishes the transport of some, but not all substrates (see page 451, 1st column last paragraph). Further Letschert teaches

mutations do not alter transport (substrate specificity) of all molecules studies. This demonstrates the unpredictability of this technology area; clearly there is no universal association between polymorphisms in OATP8 and substrate specificity . There is no evidence on the record that the polymorphism at position 811 of SEQ ID NO: 16 is associated with change of function of the encoded polypeptide, or that the alleles present at this location are predictive of any disease or disorder.

There is also a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. The art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state or a physiological state. For example, Hacker et al. were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the β-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). Finally, in some cases where multiple polymorphisms are identified in a gene, some of these are demonstrated to be disease associated and some are not. Thus, even for

SNPs within the same gene, it is highly unpredictable as to whether a particular marker will be disease associated.

The significance of the instantly disclosed OATP8 polymorphism remains highly unpredictable. Thus determining how to use the claimed methods as asserted by applicant, requires the knowledge of unpredictable and potentially non-existent associations between the polymorphism and some disease or disease state. Even if the elected polymorphism is in some way associated with some disease, it is difficult (if not impossible) to know or predict from the teachings of the specification which disease or how the polymorphism is associated. That is, it is unpredictable as to whether the presence of a particular allele the polymorphism would confer a higher or lower likelihood of having the disease. In this case, the possible uses for the claimed methods are undefined, beyond the suggestion that they can be used to detect a disease associated with the OATP8 gene prior to treatment with a OATP8 drug. Furthermore, even when a relationship between the polymorphism and a disease state or response to treatment is noted in an isolated population, it is still unpredictable as to whether this indicates that the disease is mediated by the OATP8 gene or if it is merely a marker for the disease state.

The quantity of experimentation required to discover how to use the instant invention is very high. In order to use the claimed invention as asserted by the specification, one would have to establish a relationship between the polymorphism at nucleotide 811 of SEQ ID NO: 16 some disease state or some disease treatment method. Indeed, even to use the method of claim 1 to identify patients suited for

particular pharmaceutical agents or to predict a disease, one would need to know that the polymorphism at nucleotide 811 of SEQ ID NO: 16 was in some way associated with response to some pharmaceutical agent or some disease. In order to obtain the type of information necessary to practice the claimed invention, one would be required to undertake the screening of hundreds or thousands of patients as well as possible hundreds of diseases or pharmaceutical agents. Even if such experiments were undertaken, it would still be unpredictable as to whether any associations would be detected, in light of the unpredictability of such associations, as already discussed. Thus, while one could perform further research to determine whether applicant's method would be useful in disease detection and/or treatment, it is unknown as to what the outcome of such research might be and as to whether any quantity of experimentation would result in the identification of an association between the OATP8 811 polymorphism and any disease or condition. Further, absent a teaching the polymorphism at position 811 of SEQ ID NO: 16 is not associated with such conditions, it is further unpredictable as to whether detection of the polymorphism would be useful in predicting, e.g., the absence or decreased likelihood of such conditions.

Conclusion

Thus, in light of the nature of the invention, the state of the art, the high level of unpredictability in the art, the lack of direction or working examples in the specification, and the high quantity of experimentation that would be required to practice the claimed invention, it is concluded that undue experimentation would be required to use the instantly claimed invention. Thus, although the specification certainly enables one to

detect the presence of the polymorphism(s) (i.e. the "make" portion of 112 1st paragraph), it would require undue experimentation in order to determine how to use the claimed invention.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Laubert et al. (WO 98/45436, pages 1-54 , and SEQ ID NO1 page 1 of the sequence listing).

With regards to claims 1, 2, Laubert et al. teach sequencing of human Atnov (see page 14, line 6), and further teach a method which comprises sequencing a polynucleotide which includes determining the sequence of a human Atnov nucleotide sequence at position 811 of SEQ ID NO: 16, namely, Laubert et al. teach a "G" at this position (SEQ ID NO: 2 taught by Laubert et al.). Laubert et al. teach a method which comprises sequencing their SEQ ID NO: 1, which comprises at least nucleotides 1 to 890 of instant SEQ ID NO: 16, including position 811 (see nucleotides 848-907 of SEQ ID NO: 1 taught by Laubert et al.).

With regards to claim 3, Laubert et al teach the use of RFLP to detect sites of polymorphisms (see page 15, lines 24-26).

Summary

No claims are allowed.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

J. Goldberg

JEANNE A. GOLDBERG
PRIMARY EXAMINER
12/22/06

Steven Pohnert